International Journal of Gerontology 7 (2013) 142–146

Contents lists available at SciVerse ScienceDirect

International Journal of Gerontology

journal homepage: www.ijge-online.com

Original Article

Relationship Between Metabolic Scores, Systemic Inflammation, Renal Function, and High-risk Peripheral Arterial Disease☆

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ARTICLE INFO

Article history:
Received 13 September 2011
Received in revised form
11 April 2012
Accepted 14 June 2012
Available online 23 December 2012

Keywords:
metabolic scores,
peripheral artery disease,
systemic inflammation,
renal function

SUMMARY

Background: Metabolic syndrome (MS) associated with systemic inflammation identifies high-risk cardiovascular diseases (CVDs). Deteriorated renal function leads to poor cardiovascular outcomes. However, the relationship between such metabolic anomaly, systemic inflammation and renal function in patients diagnosed with peripheral arterial disease (PAD) remains largely unknown.

Materials and methods: A total of 249 consecutive individuals meeting the study criteria from our outpatient clinics were enrolled in the study. Baseline demographic data and information regarding metabolic abnormalities [presented as Adult Treatment Panel (ATP) III scores], high-sensitivity C-reactive protein (Hs-CRP) level, and estimated renal function [calculated by the Modification of Diet in Renal Disease (MDRD) method] were obtained. High-risk PAD was defined by utilizing the ankle–brachial index (ABI) method.

Results: Of all 249 subjects, 60 had diagnostic high-risk PAD. The prevalence of PAD increased in a significant trend with worsening ATP III scores. By utilizing a multivariate adjustment model, body mass index and worse renal function were independently associated with PAD (both $p < 0.05$). A receiver operating characteristic (ROC) curve showed that estimated glomerular filtration rate (eGFR) and Hs-CRP superimposed on metabolic scores (Mets) well expanded the area under the curve from 0.646 to 0.743 (c-statistics: 0.015) in identifying PAD and that the addition of eGFR on Mets and Hs-CRP further increased the model significantly by likelihood ratio test ($p < 0.001$).

Conclusion: The combination of metabolic scores and systemic inflammation in terms of Hs-CRP superimposed on estimated renal function yielded better identification of patients at high risk for PAD. Our data suggested that early recognition of PAD may be enhanced in a population by screening for established higher cardiovascular risks combined with abnormal renal function.

1. Introduction

Metabolic syndrome (MS) encompassing dyslipidemia, high blood pressure, increased waist circumference, and impaired glucose metabolism linking to cardiovascular events such as acute myocardial infarction, heart failure, stroke and death, has become the leading healthy burden in the world[1–3]. MS also increases the risk of coronary artery disease (CAD) involvement in patients with peripheral artery disease (PAD)[4]. The latest study in women has shown that PAD occurs more frequently in the MS group with higher levels of inflammatory marker[5]. The Edinburgh artery study revealed a more significant relationship between MS and cerebrovascular disease than MS and PAD[6]. Renal function impairment was the leading negative prediction factor after vascular surgery in PAD[7]. However, the relationship and potential interactions between PAD, systemic inflammation, and renal functional status remains uncertain in MS.

2. Materials and methods

The patients participating in this single-center study were recruited from cardiovascular outpatient clinics at Mackay Memorial Hospital from July to December, 2009. The study design was

☆ All contributing authors declare no conflicts of interest.

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1873-9598/$ – see front matter
http://dx.doi.org/10.1016/j.ijge.2012.11.016

approved by the local ethics committee in accordance with the Declaration of Helsinki. In brief, 420 consecutive patients (age 50–69 years) presented at our outpatient clinics with a high risk for PAD including those with a history of smoking or diabetes, elderly individuals with at least one known cardiovascular risk, patients with symptomatic leg claudication or ischemic rest pain, known coronary artery diseases and known carotid or renal artery diseases received screening for the possible existence of PAD by utilizing the ankle–brachial index (ABI) artery blood pressure ratio method[8]. Patients with known cardiovascular surgery history or the presence of rheumatic heart disease, atrial fibrillation, previous implantation of a pacemaker and overt renal insufficiency (creatinine > 2.5 mg/dL) or with dialysis history were all excluded in our study. Of the 420 patients, 249 individuals without overt decompensated systolic heart failure (B-type Natriuretic Peptide (BNP) less than 200 pg/dL and ventricular ejection fraction more than 50%) were included in our final analysis.

Of the 249 patients, 60 had diagnostic high-risk PAD according to the ABI definition. Because a previous study had shown that the diagnostic criterion for PAD with ABI <1.0 bore the same poor prognosis as that with ABI <0.9, we prespecified the definition of PAD as ABI <1.0 or ABI >1.3[9]. A detailed review of medical history by two experienced cardiologists with physical examination and electrocardiography (ECG) were all performed. All baseline characteristics and related anthropometrics including age, body height, weight, body mass index (BMI), and waist circumference were acquired with routine laboratory data including hepatic, renal and lipid profiles. Echocardiography was performed in patients with significant heart murmur. History of diabetes (DM) was defined as a fasting blood glucose level of more than 126 mg/dL or any current usage of diabetes medication with previously diagnosed DM. Patients who had a hypertension history, were taking anti-hypertension agents or had a systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥ 90 mmHg were diagnosed as having hypertension. Renal function was evaluated as the serum creatinine level (mg/dL) and estimated glomerular filtration rate (eGFR) by the Modification of Diet in Renal Disease (MDRD)-Simplify method. Coronary artery disease was defined as a known myocardial infarction history or significant coronary stenosis with percutaneous intervention, including stent deployment. According to the Adult Treatment Panel (ATP) III and modified Taiwan guideline, the metabolic syndrome score (Mets) was defined as the presence of any of following traits: abdominal obesity, defined as waist circumference >90 cm in men and >80 cm in women; serum triglyceride >150 mg/dL or drug treatment for hypertriglycemia; serum high-density lipoprotein cholesterol (HDL-C) <40 mg/dL in men and <50 mg/dL in women; blood pressure >130/85 mmHg or drug treatment for hypertension; fasting plasma glucose (FPG) >100 mg/dL or drug treatment for elevated blood sugar[10].

The C-reactive protein (Hs-CRP) level was determined by a highly sensitive, latex particle-enhanced immunoassay using Elecsys 2010 (Hitachi Corp. Hitachinaka Ibaraki, Japan). Serum samples were collected using standard sampling tubes or tubes containing separating gel. After ensuring individualized patient samples, calibrators and controls were at ambient temperature (20–25 °C) and the measurement was taken within 2 hours because of possible evaporation effects.

2.1. Statistical analysis

Continuous data were presented as mean ± standard deviation and were compared with *t* test or nonparametric test (Mann–Whitney *U* test) between groups. Categorical items or data expressed as proportion ratio were compared by a Chi-square test or Fisher's exact test. Baseline continuous data or variables were compared by a Wilcoxon nonparametric test for significant trend across tertile groups. A receiver operating characteristic (ROC) curve was used to evaluate the area under the curves in identifying high-risk PAD with c-statistics used for comparison between different models. The likelihood ratio test post-estimation was used to compare whether a variable added to a previous model would significantly expand the whole model in the clinical diagnosis of PAD. Interaction terms were used to test the potential interactions between two continuous independent variables in the association with PAD as the binary dependent variable.

All data was analyzed with the software STATA 8.0 package (Stata Corp, College Station, Texas, USA). A p value was set at two-tailed probability and $p < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics and demographic data

Baseline characteristics of the 249 enrolled individuals are listed in Table 1. Patients with PAD ($n = 60$) tended to be older (68 ± 13.9 years vs. 63 ± 10.9 years), had higher body weight (69 ± 16.1 kg vs. 63.5 ± 13.7 kg), larger waist circumference (89.7 ± 12.6 cm vs. 84.3 ± 15.5 cm), higher prevalence of diabetes (43% vs. 25%)/metabolic syndrome (65% vs. 45.5%), lower HDL-cholesterol level (44.4 ± 11.1 mg/dL vs. 49 ± 14.3 mg/dL), lower renal eGFR levels (65.6 ± 28.9 mL/minute/1.73 m^2 vs. 86.1 ± 27.3 mL/minute/1.73 m^2) and a borderline higher prevalence of CAD (33.3% vs. 21.2%, $p = 0.055$) when compared to those in the non-PAD group ($n = 189$). When all 249 enrolled participants were further divided into three ordered groups in terms of renal function (eGFR <60 mL/minute/1.73 m^2, ≥60 and <90 mL/minute/1.73 m^2, and ≥90 mL/minute/1.73 m^2), there was a trend toward increasing age (trend $p < 0.0001$), higher blood pressure (trend $p = 0.01$), higher fasting glucose (trend $p < 0.0001$), higher triglyceride level (trend

Table 1
Baseline demographics data by PAD.

	No PAD ($n = 189$)	PAD ($n = 60$)	p
Age (y)	63 ± 10.9	68 ± 13.9	0.004
Female/male (%)	106/83 (56/44)	36/24 (60/40)	0.2
SBP (mmHg)	134.3 ± 29.6	142.9 ± 25.5	0.054
DBP (mmHg)	78.2 ± 18	79.3 ± 12.6	0.68
Body weight (kg)	63.5 ± 13.7	69 ± 16.1	0.011
BMI (kg/m^2)	25 ± 4.6	27.7 ± 6.9	<0.001
Waist (cm)	84.3 ± 15.5	89.7 ± 12.6	0.015
Hypertension history, yes/no (%)	143/46 (76/24)	44/16 (73/27)	0.716
Diabetes history, yes/no (%)	47/142 (25/75)	26/34 (43/57)	0.006
Hyperlipidemia history, yes/no (%)	70/119 (37/63)	29/31 (48/52)	0.12
CAD history, yes/no (%)	40/149 (21.2/78.8)	20/40 (33.3/66.7)	0.055
Metabolic syndrome, yes/no (%)	86/113 (45.5/54.5)	39/21 (65/35)	0.008
AC sugar (mg/dL)	115 ± 35.2	128.7 ± 52.1	0.022
Cholesterol (mg/dL)	196.3 ± 46.9	188.5 ± 45.7	0.264
HDL-C (mg/dL)	49 ± 14.3	44.4 ± 11.1	0.029
LDL-C (mg/dL)	115.8 ± 36.2	117.3 ± 30.4	0.77
Triglyceride (mg/dL)	143.9 ± 103.1	169 ± 121.8	0.117
eGFR (mL/min/1.73 m^2)	86.11 ± 27.3	65.6 ± 28.9	0.0041
Hs-CRP(mg/dL)	0.21 ± 0.29	0.59 ± 1.25	0.0001

PAD was defined by ankle–brachial pressure index >1.3 and <1.0.
AC sugar = fasting blood sugar; BMI = body mass index; CAD = coronary artery disease; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; Hs-CRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; PAD = peripheral arterial disease; SBP = systolic blood pressure.

$p < 0.0001$) and a borderline increased prevalence of diabetes history (trend $p = 0.05$) (Table 2). In addition, the ABI value also decreased in an ordered fashion across worse renal profiles ($p = 0.02$ for the right and $p = 0.01$ for the left side, respectively).

3.2. Metabolic scores, renal function and inflammation

The prevalence of PAD and impaired renal function were increased in a significant trend with higher metabolic scores. The metabolic score was higher compared with impaired renal function and level of inflammation marker Hs-CRP (Fig. 1). By multivariate adjustment model, body waist, BMI and renal function in terms of eGFR were all independently associated with PAD (all $p < 0.05$) though history of diabetes and smoking behavior both showed borderline association with PAD ($p \geq 0.05$ and <0.1) (Table 3). Data from ROC showed that Hs-CRP superimposed on the existence of Mets well expanded the model further from 0.679 to 0.714 (Fig. 2). Impaired renal function in terms of eGFR was also independently related to PAD but had no incremental effect when superimposed on the combination of Hs-CRP and Mets by c-statistics test. However, impaired renal function had a significantly increased model prediction of PAD when added onto inflammation marker and Mets with respect to the prevalence of PAD (Table 4 and Fig. 3). Finally, there was no evidence of significant effect modification by systemic inflammation on the relationship between renal function and Mets in identifying the prevalence of PAD except for a borderline interaction between Mets and renal function ($p = 0.071$ for interaction term) (Table 3).

4. Discussion

In this study, we demonstrated that patients at high risk for PAD had higher chances of metabolic derangement, which was linked to systemic inflammation and impaired renal function. While both Mets and inflammation markers in terms of Hs-CRP identified high-risk PAD subjects well, the addition of renal function further significantly enhanced the diagnostic model of PAD.

Table 2
Baseline demographic data by renal function.

	eGFR <60 ($n = 53$)	eGFR ≥60 and < 90 ($n = 99$)	eGFR ≥90 ($n = 97$)	p
Age (y)	69.4 ± 11	61.8 ± 12.1	55.3 ± 10.4	<0.0001
Female/male (%)	30/23 (56.6/43.4)	48/51 (48.5/51.5)	64/33 (66/34)	0.13
BMI (kg/m^2)	25.7 ± 3.7	25.9 ± 4.1	26.6 ± 3.8	0.99
Waist (cm)	87.8 ± 11.5	86.9 ± 9.8	86.4 ± 15.7	0.16
SBP (mmHg)	136.8 ± 21.6	131.1 ± 18.6	131.7 ± 18.7	0.01
AC sugar (mg/dL)	134 ± 50.6	113.6 ± 34.8	114.2 ± 36.9	<0.0001
Cholesterol (mg/dL)	192.3 ± 46.6	193.8 ± 38.6	201.9 ± 49	0.14
Triglyceride (mg/dL)	201.4 ± 85.8	145 ± 85.4	126.9 ± 83.5	<0.0001
LDL-C (mg/dL)	118 ± 37.5	117 ± 33.6	111.3 ± 31.9	0.25
HDL-C (mg/dL)	46.5 ± 14.1	46.5 ± 13.2	49.8 ± 12.8	0.06
CHF history, yes/no (%)	35/18 (66/34)	55/44 (55.6/44.4)	53/44 (54.6/45.4)	0.22
Hypertension history, yes/no (%)	39/14 (73.6/26.4)	78/21 (78.8/21.2)	70/27 (72.2/27.8)	0.69
Diabetes history, yes/no (%)	26/27 (49.1/50.9)	19/80 (19.2/80.8)	28/69 (28.9/71.1)	0.05
Right ABI	1.06 ± 0.16	1.08 ± 0.12	1.11 ± 0.1	0.02
Left ABI	1.03 ± 0.15	1.05 ± 0.11	1.09 ± 0.08	0.01
Hs-CRP (mg/dL)	0.38 ± 0.54	0.32 ± 0.98	0.26 ± 0.31	0.42

ABI = ankle–brachial index ratio; AC sugar = fasting blood sugar; BMI = body mass index; CHF = congestive heart failure; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; Hs-CRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure.

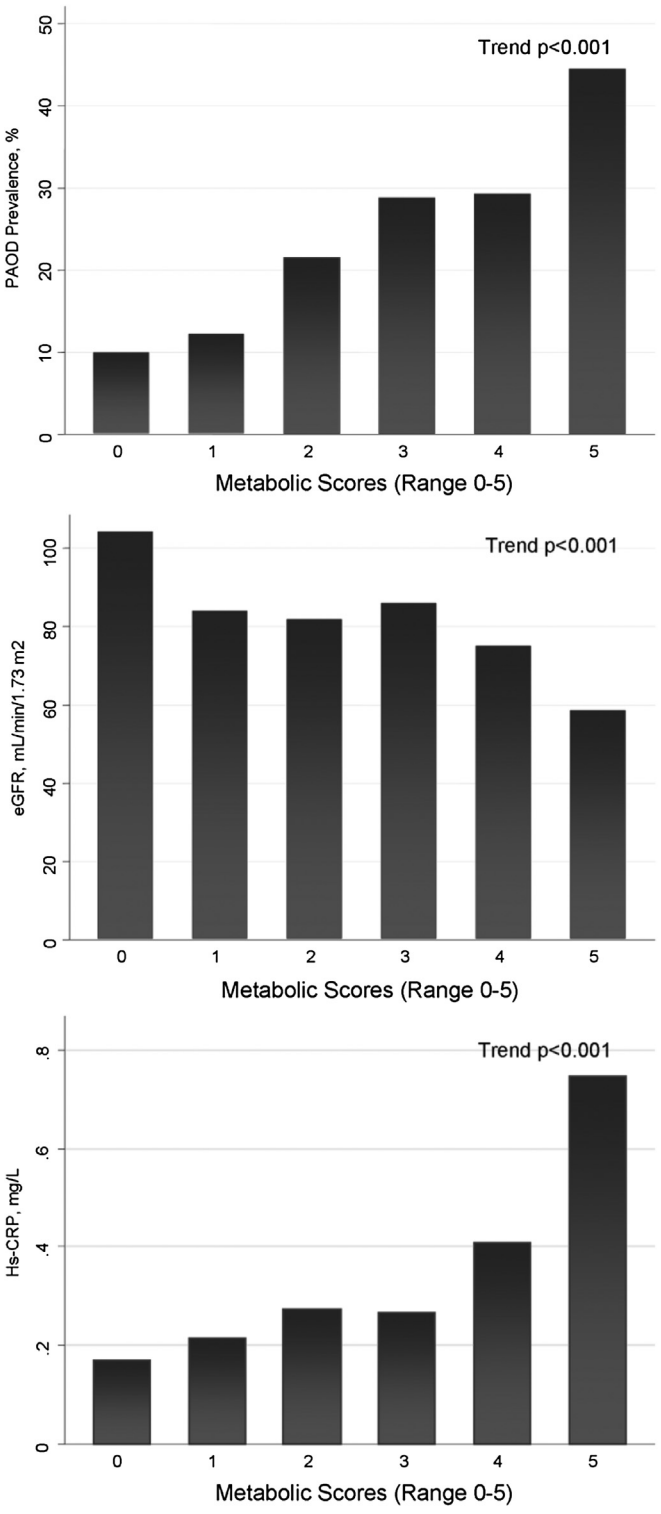

Fig. 1. With higher metabolic scores, there is an ordered increase of peripheral arterial disease (PAD) prevalence and plasma high-sensitivity C-reactive protein (Hs-CRP) level (all $p < 0.001$). Renal function as estimated glomerular filtration rate (eGFR) was also observed to deteriorate in a significant trend across higher metabolic scores (trend $p < 0.001$).

A previous study has established the relationship between metabolic syndrome (MS) and atherosclerotic vascular lesions in coronary, carotid and femoral arteries[11]. Though some authors debate on the causal link between MS and the development of

Table 3
Multivariate logistic regression model.

Variables	Odds ratio	*p*	95% confidence interval
With body waist			
Age (y)	1.02	0.209	0.99–1.05
Female/male (%)	0.46	0.087	0.19–1.12
Waist (cm)	1.03	0.045	1.0001–1.06
Hypertension history, yes/no (%)	0.72	0.405	0.33–1.57
Diabetes history, yes/no (%)	2.0	0.05	1.001–3.99
Current smoker, yes/no (%)	2.46	0.053	0.99–6.14
Cholesterol (mg/dL)	1.0	0.576	0.99–1.006
HDL-C (mg/dL)	0.98	0.108	0.95–1.005
eGFR (mL/min/1.73 m^2)	0.99	0.035	0.97–0.999
With body mass index			
Age (y)	1.03	0.115	0.99–1.06
Female/male (%)	0.59	0.24	0.24–1.43
BMI (kg/m^2)	1.13	0.002	1.05–1.22
Hypertension history, yes/no (%)	0.67	0.301	0.29–1.46
Diabetes history, yes/no (%)	1.92	0.071	0.94–3.89
Current smoker, yes/no (%)	2.46	0.06	0.96–6.27
Cholesterol (mg/dL)	1.0	0.617	0.99–1.007
HDL-C (mg/dL)	0.98	0.149	0.95–1.008
eGFR (mL/min/1.73 m^2)	0.99	0.043	0.97–0.999

BMI = body mass index; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol.

PAD[12], Wei and Yaunxi observed that patients with MS did have higher chances of developing PAD in the elderly Chinese population and may warrant repeated ABI measures in order to monitor the disease progress[13,14]. Furthermore, the recent Smart study has built up the association between MS, vascular events and all-cause mortality[1].

David et al disclosed that the inflammation was linked to MS and risk of symptomatic PAD in the female population[5]. Low-grade inflammation may in part mediate one of the pathogenesis pathways between MS and coronary/peripheral artery atherosclerosis[15].

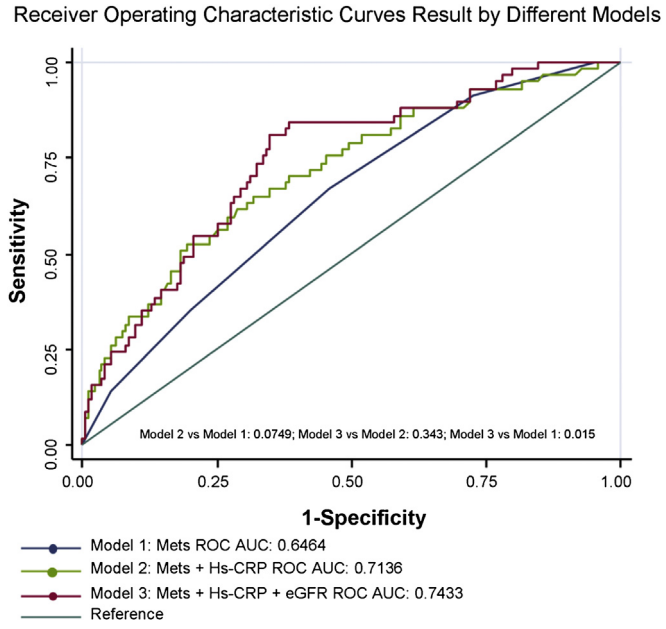

Fig. 2. Receiver operating characteristic curve (ROC) from metabolic scores (Mets), high-sensitivity C-reactive protein (Hs-CRP) and renal function in terms of estimated glomerular filtration rate (eGFR) in the identification of peripheral arterial disease (PAD) with individualized discrimination ability shown by using c-statistics. The composite of renal function and Hs-CRP was shown to add incremental value significantly beyond Mets alone in identifying PAD (c-statistics: 0.015).

Table 4
Odds ratio and significance of metabolic scores, Hs-CRP and renal function and interaction terms.

Variables	Odds ratio (95% confidence interval)	Standard error	*p*
Mets	1.81 (1.30–2.52)	0.31	<0.0001
Hs-CRP	16.41 (1.52–177.2)	19.92	0.021
Interaction of Mets and Hs-CRP	0.61 (0.32–1.19)	0.21	0.147
eGFR	0.97 (0.96–0.99)	0.008	0.001
Hs-CRP	1.12 (0.2–6.23)	0.98	0.899
Interaction of eGFR and Hs-CRP	1.02 (0.99–1.04)	0.013	0.149
Mets	0.71 (0.35–1.44)	0.26	0.343
eGFR	0.96 (0.93–0.99)	0.015	0.007
Interaction of Mets and eGFR	1.009 (1–1.02)	0.0049	0.071

eGFR = estimated glomerular filtration rate; Hs-CRP = high-sensitivity C-reactive protein; Mets = metabolic scores.

In previous studies, ß2M, cystatin C, Hs-CRP, and glucose level were identified as the strongest biomarkers beyond traditional risk factors for subjects with PAD and conferred the pathogenesis of renal endothelial cell dysfunction linked to PAD[16]. Some investigators noticed that a higher prevalence of intermittent claudication symptoms existed in the presence of PAD with more Mets components in terms of abdominal obesity and elevated fasting glucose level[17]. Metabolic score has also been shown to be inversely linked to HDL-C[18], but the relationship between metabolic score and early-stage kidney disease in PAD remained elusive. In our study, we had similar observations and further expanded the finding that impaired renal function superimposed on systemic inflammation in terms of Hs-CRP and metabolic score has resulted in a better identification of subjects at risk for PAD.

Of no doubt, renal functional impairment and high NT-pro BNP level were robust predictors for all-cause and cardiovascular-related mortality in subjects with CAD and PAD[19]. In the BARI

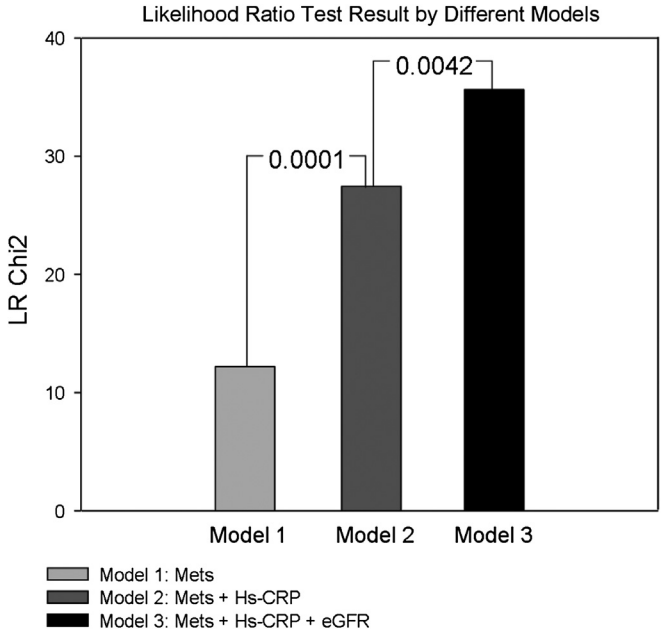

Fig. 3. The likelihood ratio test comparing different models showed that when renal function was added onto metabolic scores (Mets) and high-sensitivity C-reactive protein (Hs-CRP), the model was enhanced significantly for identifying peripheral arterial disease (PAD).

study, chronic kidney disease was a strong independent predictor for recurrent hospitalization, subsequent coronary artery bypass surgery, and mortality in patients with multiple-vessel CAD when accompanied by diabetes[7]. Furthermore, impaired renal function may seem to have greater impact on long-term clinical survival, limb salvage rates, and graft patency rates in more advanced PAD[20,21]. Patients with CAD and end-stage renal disease (ESRD) tended to have worse cardiovascular outcomes[22], and even mild renal impairment may aggravate the clinical metabolic abnormality via low-grade inflammation and glomerular endothelial cell dysfunction in PAD[23]. However, composition of eGFR and microalbuminuria was effective for identifying patients at high risk of cardiovascular events along with PAD[24]. Chronic renal insufficiency (microalbuminuria or eGFR <60 mL/minute/1.73 m^2) was shown to be a stronger prognosticator than metabolic scores in Japanese people with diabetes and PAD and remained powerful in predicting all-cause mortality, which provided a clue that worsened renal function not only plays a role in the pathogenesis of PAD but may also be a key factor in determining outcomes[25,26]. In the present study, we observed a similar relationship between metabolic abnormality, systemic inflammation, chronic renal impairment and PAD. Patients with chronic renal disease (CKD) usually become progressively malnourished with low levels of albumin, prealbumin, and transferrin implying activation of the inflammation mechanism[27]. Dyslipidemia combining with angiotensin II-mediated alternations in endothelial cell function stimulate and amplify the effect of inflammation and further cardiovascular disease[28]. In short, composite of renal dysfunction, metabolic derangement, and systemic inflammation yield an even better identification of subjects at risk for PAD.

5. Limitations

First, this is a retrospective, single-center study. Second, the data analysis came from a cross-sectional survey which lacked longitudinal follow-up. More large-scaled, prospective studies may be helpful to further address the causal relationship between renal function and PAD independent of traditional cardiovascular risks in the future. Third, though ABI as a noninvasive screening test in the document of high-risk PAD patients may be less accurate than invasive lower extremity angiography, such measure has been well validated by correlation with angiography[29] and outcomes method[8].

6. Conclusion

The combination of Mets and systemic inflammation in terms of Hs-CRP superimposed on estimated renal function yielded better identification of individuals at high risk for PAD. The present study suggested that early recognition of PAD may be enhanced in a population by screening established higher cardiovascular risks combined with abnormal renal function.

Acknowledgments

This work was supported by research grants from Mackay Memorial Hospital, Taipei, Taiwan.

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